REMARKS

The Office Action has rejected Claims 20-28, 32-34, 52, 56, 63-67 under 35 USC § 103 as defining subject matter which is allegedly rendered obvious by the teaching in U.S. Patent No. 6,096,712 to Szelke, et al. ("Szelke, et al."). The Office Action has additionally rejected Claims 20-23 under USC § 103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,368,788 to Kozhemyakin et al. ("Kozhemyakin et al."). Claims 20-23 are also rejected under 35 USC § 103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,716,810 to Brennan et al. ("Brennan et al."). Finally, Claim 20 is rejected under 35 USC § 103 as defining subject matter which is allegedly rendered obvious by the teachings of U.S. Patent No. 5,696,116 to Clozel et al. ("Clozel et al.").

Applicant has amended claims, cancelled others and has added claims to the application, which amendments, when considered with the Remarks hereinbelow, are deemed to place the present application in condition for allowance. Favorable action is respectfully requested.

The claims have been amended to emphasize the subject matter which is preferred. Support for the amendments is found in the instant specification, For example, Claim 20 has been amended to restrict n to 1. Support for n being 1 is found on Page 25, Line 20 of the instant specification. Moreover it should be noted that applicant has amended Claim 20 by specifically reciting the electron withdrawing groups and electron donating groups. Support for the amendment to Claim 20 is found on Page 20, lines 7-31 of the instant specification. In view of this amendment, R and R_1 cannot include peptides or other amino acids. Further Claim 20 has been amended to restrict the scope thereof to R being aryl lower alkyl, which may be

unsubstituted and substituted on the aryl moiety with an electron withdrawing group or electron donating group and R_1 being lower alkyl which may be unsubstituted or substituted with an electron withdrawing group or electron donating group. Support is found on page 25, line 31 to page 26, line 12 of the instant specification. The definitions of R_2 and R_3 have also been narrowed. Support is found on page 15, line 26 to page 17, line 29, page 23, line 1 to page 25, line 30 of the instant specification.

Further, there is support for R_3 in Claim 20 excluding hydrogen from its definition. Again support is found in the instant application. Attention is directed to Claim 21 as originally filed, which states that one of R_2 and R_3 is hydrogen; this means that the other is not hydrogen. Thus, there is support in the application for one of R_2 and R_3 being other than hydrogen. Thus, applicant has amended the claims so that R_3 excludes hydrogen from its definition. Claims 25-27 have been amended to be consistent with the claimed subject matter in Claim 20. Support for the amendment in Claim 63 is found on Page 26, line 24 to Page 27, line 16 of the instant specification.

The remaining pending claims have been amended to be consistent therewith.

Applicant has also added Claims 73-103 to the application. Support for Claim 73 is found in original Claim 63. Support for Claim 74 is found on Page 25, lines 31-32 of the present specification, while support for Claim 75 is found on Page 26, lines 11-12 of the specification. Further, support for Claims 76-85 is found on Page 26, line 24 to Page 29, line 16 of the instant application. Applicant has also added Claims 86-103 to the instant application, which is supported by the disclosure on Page 25, Line 10 to Page 29 line 16 of the instant specification. Support for Claims 90-107 is found on page 20, line 1 to page 23, line 23 and page 24, line 3 and page 27, line 10 of the instant application.

These amendments also cancelled claims. Applicants have not abandoned this subject matter in these deleted claims and reserve the right to file a continuation application directed thereto.

No new matter is added to the application. Moreover, these amendments were made to direct the claimed subject matter to the preferred embodiments.

Pursuant to the rejection of Claims 20-28, 32-34, 52, 56, and 63-67 under 35 USC § 101, the United States Patent and Trademark Office alleges that the utility for the prophylaxis of migraine headaches is unbelievable.

It is respectfully submitted that the United States Patent and Trademark Office has not made out a prima facie case. Case law has held that applicant's assertion of utility creates a presumption of utility sufficient to satisfy the utility requirement of 35 USC § 101. In re Langer, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974).

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to questions the objective truth of the statement of utility or its scope.

Id, 503 F.2d at 1391, 183 USPQ at 297 (emphasis in original).

Case law has held that the Examiner has the initial burden to show that one of ordinary skill in the art would reasonably doubt the asserted utility. In re Swartz, 232 F.3d 862, 863, 56 USPQ 2d 1703, 1704 (Fed Cir 2000). Only after the Examiner has presented evidence that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility. Id.

In the present case, the United States Patent and Trademark Office has not provided any evidence that the compounds described in the underlying application cannot be used for the prophylaxis of migraine headaches. It did not cite any publications that teach or even suggest that the compounds described in the above-identified application cannot be useful for the proplylaxis of migraine. It did not provide any scientific evidence that refutes applicant's utility. All it presented was an argument that prophylaxis requires 100% success and that anything less than 100% success does not meet the statutory requirements under 35 USC § 101. But these are merely arguments set forth by the United States Patent and Trademark Office. It has not presented scientific evidence or a teaching in the literature refuting applicant's utility. Thus the United States Patent and Trademark Office has not met its burden.

Moreover, the assertion by the United States Patent and Trademark Office that a 100% success rate is required to satisfy the utility requirement under 35 USC § 101 is contrary to case law. As the Federal Circuit has held, to violate 35 USC § 101, the claimed invention must be totally incapable of achieving a useful result. Brooktree Corp v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571, 24 USPQ2d 1401, 1412, (Fed. Cir. 1992). As stated in MPEP §2107.01, "A small degree of utility is sufficient... If an invention is only partially successful in achieving a useful need a rejection of the claimed invention as a whole based on lack of utility is not appropriate." Thus, 100% success rate is not required to meet the statutory requirements of 35 USC § 101. Thus, the United States Patent Office has not provided the correct standard in the first instance to sustain a rejection under 35 USC § 101.

Moreover it is not unreasonable to one of ordinary skill in the art that a drug is capable of preventing migraine headaches. Attention is directed to page 8 of the attached publication regarding Inderal ®. As described therein Inderal ® is indicated for the prophylaxis of common

migraine headaches. This is not the only example. As a further example, attention is directed to the publication regarding Sansert ®. As shown on page 2, one of the indications of this drug is the prevention of vascular headaches in certain patients. These are just two examples to illustrate the point it is credible that a drug can be useful for the prophylaxis of migraines, contrary to the allegations in the Office Action.

Thus for the reasons provided, the rejection of the claimed subject matter under 35 USC § 101 is obviated; withdrawal thereof is respectfully requested.

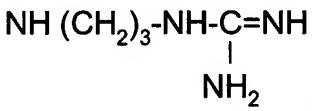
In support of the rejections of Claims 20-23, 25 under 35 USC § 103 the Office Action cites Szelke et al.

Szelke et al. disclose kininogenase inhibiting peptides and analogues thereof with the C-terminal related to agmatine or noragmatine. It discloses that in general, the main indications for kininogenase inhibitors include such indications, inter alia, as migraines. But, it never specifically discloses that the compounds therein are useful for the treatment or prophylaxis of migraines. Thus, Szelke et al. fail to teach that the compounds therein are useful for the prophylaxis of migraines.

The Office Action refers to Examples 331 and 332 which have the structures Ac-D-Ile-Nal-Nag, and Ac (4-I) DPhe- 1 – Nal – Nag, respectively.

The examples are not structurally related to the compounds utilized in the present invention. For example, such structures require three linear amide bonds, one between the acetyl group and the Ile, and another between Phe and – Nal, and the last one between the Nal and the NH group of the Nag. On the other hand in the compounds utilized in the present invention, there is no amide bond linkage between R and the NH group or between R_1 and the acyl group. As defined, R is unsubstituted or substituted aryl lower alkyl, and R_1 is defined as unsubstituted

or substituted lower alkyl. Thus, there is no peptide linkage between the acyl group and R_1, or between R and the NH group.

Moreover, it is noted that the substituent at the carboxy end of the compounds in Szelke et al., is;  however, the compounds used in the present invention do not include such group. More specifically, as defined, the R_1 substitution, which is the substitution at the carboxy end of the molecules, does not include such a substituent or any group similar thereto.

Thus, the compounds used in the present invention for the treatment of prophylaxis of migraines are not structurally similar to the compounds disclosed in Szelke et al. Further, Szelke et al. do not teach, disclose or suggest the use of compounds utilized in the present specification or similar compounds thereto for the treatment or prophylaxis of migraines. Moreover, as indicated hereinabove, Szelke et al. do not teach, disclose or suggest a drug for the treatment or prophylaxis of migraines.

Therefore, for the reasons provided, the rejection of Claims 20-23 and 25 under 35 USC § 103, is obviated withdrawal thereof is respectfully requested.

In support of the rejection of claims 20-23 under 35 USC § 103, the Office Action cites Kozhemyakin et al. In particular, the Office Action cited the compound Ac-Glu-Trp, alleging that R_1 is methyl and R is methyl that is substituted once with carboxyl and once with indolymethyl.

Again this compound is not structurally similar to the compounds used in the present invention. For example, the compound of Kozhemyakin et al. is a linear peptide containing a

peptide linkage between two amino acids. However, as defined the compounds used in the present invention do not contain a peptide linkage between R and the amino group or between the acyl group and R_1. As defined, R and R_1 cannot be an amino acid or contain an amino acid. More specifically, as defined R_1 is unsubstituted or substituted lower alkyl and R is unsubstituted or substituted aryl lower alkyl, neither of which are amino acids as defined. Further, neither R nor R_1 contain an amino acid substituent. Therefore, as defined the compounds used in the present invention do not contain a peptide bond between the R group and the amino group or between the R_1 group and the acyl group. Consequently the compounds used in the present invention cannot have the formula Ac-Glu-Trp or any product that is structurally related or similar thereto. Thus, the teaching of Kozhemyakin et al. do not render obvious the subject matter in Claims 20-23. The rejection thereof under 35 USC § 103 is obviated, withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 20-23 under 35 USC § 103, the Office Action cites Brennan, et al.

Brennan et al. disclose N-acetylated peptides that are cyclic or acyclic. The compounds disclosed therein contain several amino acids. According to the Office Action, the claims are rendered obvious for the case of "R" representing hydrogen that is substituted with EWG/EDG. The Office Action also alleges that the compounds can be used to treat migraines.

Applicants disagree that the teachings in Brennan et al. render obvious the subject matter of the present invention. First, contrary to the allegations in the Office Action, Brennan et al. are not directed to treating migraines. In Column 55, line 25 of Brennan et al., referred to in the Office Action, it is stated that the compounds therein are useful in reducing body weight and for reducing weight gain in an animal and/or treating or ameliorating obesity in patients at risk for or

suffering from obesity which is caused by a side effect, from a pharmaceutical. This passage refers to conditions in which a physician would prescribe a pharmaceutical and it includes treating migraines. But, the pharmaceutical referred to therein are not the compounds of Brennan et al. but other drugs. In other words the passage referred to in the Office Action refers to the drugs of Brennan et al. being used to combat increases and decreases in weight gain resulting from the side effects of a drug being used to treat migraines, for example. Nowhere does Brennan et al.. teach or suggest that the compounds therein are useful for treating migraines. Thus, the utility of the compounds in Brennan et al. are totally unrelated to the utility recited in the claims.

Moreover, the compounds utilized in Brennan et al. are not structurally related to the compounds used in the present invention. The compounds in Brennan et al. contain many linear amino acids with several linear peptide bonds. However, as defined in the compounds utilized in the present invention, R and R_1 are not amino acids and do not contain amino acids. Moreover, there is no peptide bond between the amino group and R and the acyl group and R_1. Thus, the compounds in Brennan et al. are structurally quite different from the compounds utilized in the present invention. Moreover, the compounds utilized in Brennan et al. are structurally more complex than the compounds used in the present invention. Thus, Brennan et al. do not teach or suggest the use of the compounds utilized in the present invention. Consequently, the compounds therein do not render the compounds utilized in the present process obvious.

Thus, because Brennan et al. utilize compounds which do not render obvious the compounds of the present invention and because Brennan et al. disclose different utilities for the compounds therein and do not suggest the present utility, Brennan et al. do not render obvious

the subject matter of Claims 20-23 under 35 USC § 103, Thus, this rejection is obviated withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claim 20 under 35 USC § 103, the Office Action cites Clozel et al.

The Office Action refers to the compound Acetyl- (3, 3-diphenyl-D-alanine) – L – Leu – L – Asp – L – Ile – L - Trp. It alleges that Clozel et al. suggest that the above compound is an endothelin antagonist. Since Clozel et al. disclose that an increased endothelin level in blood plasma is found in migraine attacks, the United States Patent and Trademark office assumes that the above compound is useful for treating migraine.

It is respectfully submitted that Clozel et al. do not render obvious the subject matter of Claim 20 for several reasons. First, the compounds referred to are much more complex than the compounds utilized in the present invention. As indicated, the structure contains 6 linear amino acids, and 5 linear peptide bonds; on the other hand, the compounds utilized in the present invention do not contain any peptide bond between R and NH or between R_1 and the acyl group. Thus, the compound referred to is structurally unrelated and more complex than the compounds used in the present invention. Moreover, contrary to the allegations in the Office Action, Clozel et al. do not teach or suggest that endothelin antagonists are useful for treating migraine headaches. All it states that the compounds are endothelins antagonists and that are increased levels of endothelins are found in blood plasma during migraine attacks. However, there is no teaching therein that endothelin antagonists would be useful for treating migraines. For example, an increased endothelin level in blood plasma found in migraine attacks may be a manifestation of a migraine attack; that does not mean that than increased level of endothelin causes migraines or that a drug reducing the concentration of endothelins would be useful for treating or

preventing migraines. Thus, it cannot be concluded that the above-identified peptide in Clozel, et al., referred to by the Office Action, which is alleged to be an endothelin antagonist, is useful for treating migraines. And in fact, consistent therewith, Clozel et al never allege this utility.

Thus, inasmuch as Clozel et al. do not teach, disclose or suggest the compounds used in the present invention or compounds of similar structure, and because it does not teach, disclose or suggest that the compounds therein are useful for the treatment or prophylaxis of migraines, the rejection of Claim 20 under 35 USC § 103 is obviated, withdrawal thereof is respectfully requested.

Thus, in view of the Amendment to the Claims and the Remarks hereinabove, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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